T-cell receptor-driven lymphomagenesis in mice derived from a reprogrammed T cell.

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Public Summary:
The conversion of mature somatic cells into pluripotent stem cells, both by nuclear transfer and transduction with specific "reprogramming" genes, represents a major advance in regenerative medicine. Pluripotent stem cell lines can now be generated from an individual's own cells, facilitating the generation of stem cell-based therapeutics that do not trigger immune rejection. Many cell types can undergo nuclear reprogramming, leading to the question of whether the identity of the reprogrammed cell of origin has a biological consequence. Peripheral blood, containing a mixture of T, B, NK, and myeloid cell types, represents one potential source of reprogrammable cells. In this study, we describe the unique case of mice derived from a reprogrammed T cell. These mice have a unique T-cell receptor (TCR) gene in all cells, as opposed to the mixture present from normal TCR gene rearrangement occurring during immune system development. Surprisingly, approximately 50% of these mice develop spontaneous T cell lymphomas, which originate in the thymus. The lymphomas arise from developing T cells, and contain an activated form of the protein Notch1, similar to most human and mouse T-cell acute lymphoblastic lymphomas. This lymphomagenesis requires the expression of both functional portions (TCRalpha and TCRbeta) of the TCR, indicating a critical role for TCR signaling. Furthermore, inhibitors of TCR signaling suppress lymphoma growth, implicating TCR signaling as an essential component in lymphoma proliferation. The lymphomagenesis in these mice derived from a reprogrammed T cell demonstrates the deleterious consequences of misregulation of the TCR rearrangement and signaling pathways and illustrates one case of cellular reprogramming where the identity of the cell of origin has profound consequences.

Scientific Abstract:
The conversion of mature somatic cells into pluripotent stem cells, both by nuclear transfer and transduction with specific "reprogramming" genes, represents a major advance in regenerative medicine. Pluripotent stem cell lines can now be generated from an individual's own cells, facilitating the generation of immunologically acceptable stem cell-based therapeutics. Many cell types can undergo nuclear reprogramming, leading to the question of whether the identity of the reprogrammed cell of origin has a biological consequence. Peripheral blood, containing a mixture of T, B, NK, and myeloid cell types, represents one potential source of reprogrammable cells. In this study, we describe the unique case of mice derived from a reprogrammed T cell. These mice have prerearranged T-cell receptor (TCR) genes in all cells. Surprisingly, approximately 50% of mice with prerearranged TCR genes develop spontaneous T cell lymphomas, which originate in the thymus. The lymphomas arise from developing T cells, and contain activated Notch1, similar to most human and mouse T-cell acute lymphoblastic lymphomas. Furthermore, lymphomagenesis requires the expression of both prerearranged TCRalpha and TCRbeta genes, indicating a critical role for TCR signaling. Furthermore, inhibitors of multiple branches of TCR signaling suppress lymphoma growth, implicating TCR signaling as an essential component in lymphoma proliferation. The lymphomagenesis in mice derived from a reprogrammed T cell demonstrates the deleterious consequences of misregulation of the TCR rearrangement and signaling pathways and illustrates one case of cellular reprogramming where the identity of the cell of origin has profound consequences.

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